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# Non-motor features of Parkinson's disease subtypes

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## **Abstract**

Parkinson's disease is highly heterogeneous in early clinical features and later outcomes.

This fact makes classifying subgroups of PD relevant to clinical research and practice, particularly if they are prognostically relevant. Subgroups have been defined both on the basis of motor and non-motor features, and subgroups have been determined either empirically, based on clinical observation, or using data-driven analytic techniques.

Previous studies have examined both the overall number and the nature of non-motor symptoms and signs in tremor dominant compared with non-tremor dominant subtypes and longitudinal studies identify non-motor symptoms as important markers of prognosis and important defining features of PD subtypes . Autonomic features seem to preferentially affect individuals with non-tremor dominant PD-subtype early in the disease. Later in the disease cognitive disturbance distinguishes this phenotype. Pathological and neuroimaging studies provide substantial evidence for fundamental biological differences between tremor dominant and postural instability gait disorder (PIGD)/akinetic-rigid subtypes. Biomarker studies point towards non-tremor dominant PD as representing a more advanced and diffuse neurodegeneration than tremor dominant PD, encompassing dopaminergic and non-dopaminergic as well as synuclein and non-synuclein (A $\beta$ ) pathologies. This aligns with clinical studies that find a higher burden of non-motor symptoms in non-tremor dominant PD. The mounting evidence for the relevance of non-motor features in PD subtypes behooves us to begin to investigate the biological underpinnings of subtypes defined by both motor and non-motor features. This may be challenging, as PD subtypes are unlikely to be distinct, non-overlapping entities but are more likely to represent typical

phenotypes within a multidimensional spectrum resulting from variable contributions of a number of simultaneous pathological processes.

## Introduction

12, 34<sup>5</sup>, 6

Clinically, Parkinson's disease (PD) is highly heterogeneous. Identifying the clustering or co-occurrence of clinical features in groups of patients forms the basis of subtyping.

Subtypes of a disease are relevant if they predict outcome or response to treatment. .

Subtypes that do so should inform clinical research in that heterogeneity that is unaccounted for in clinical trials or etiological studies can obscure associations when different subtypes vary in their associations with an outcome measure of interest.

Subtyping may also help us to understand the biology of the disease. Thus, in a highly heterogeneous disease such as PD, subtyping is a useful strategy to guide research and ultimately clinical practice as well. <sup>7</sup>

Many efforts to define subtypes have been undertaken. Subtypes can be subdivided into those derived empirically, from clinical observation and *a priori* hypotheses as to how features of the disease are related to one another, or they may be derived without any such assumptions using a data-driven approach that divides patients into groups based on the co-occurrence of features included in the analysis (Figure 1)

Empirical subtyping systems include dividing PD into age at onset categories, major motor phenotypes, patterns of cognitive impairment and other NMS as recently described<sup>6</sup>.

Subtypes based on motor features are most commonly used. Two main strategies of

empirical motor subtyping have been used. One divides patients into either tremor dominant, postural instability gait disorder or intermediate phenotypes<sup>8</sup> and the other divides patients into tremor dominant, akinetic/rigid and mixed phenotypes.<sup>9</sup> The latter uses a broader array of non-tremor features to classify patients and different algorithms have been proposed. Cognitive subtypes describe which and how many cognitive domains are affected,<sup>10</sup> or whether predominantly frontal or posteriorly mediated cognitive functions are impaired. The ‘posterior’ subtype has been proposed to have a worse prognosis.<sup>11</sup> The approach taken by the recently published clinical NMS subtyping in PD is based on specific NMS dominant clinical phenotypes in largely untreated drug naïve as well as early treated PD cohorts.<sup>12</sup> A description of these published phenotypic groups are shown in Table 1.

Non-motor manifestations of PD are prominent and disabling aspects of the condition and we now understand that many of them precede the motor features of the disease.<sup>1</sup> Indeed, pathological staging systems for PD describe the progression of the synucleinopathy as beginning in the lower brainstem and/or olfactory bulb,<sup>2, 3</sup> areas which mediate a number of non-motor and non-dopaminergic functions. Furthermore, it has been suggested that PD may begin peripherally in the gastrointestinal tract where synuclein deposition has been identified prior to the onset of parkinsonism.<sup>13</sup> There is understandably great interest in understanding whether or not clinical features mediated by this early pathological involvement can be prognostically relevant. Indeed specific clinical descriptions of Non-Motor Symptom (NMS) dominant phenotypes, particularly in the untreated PD model, suggesting a link with the heterogeneity of the initiating neuropathological processes are

being increasingly described.<sup>4</sup> The broad clinical phenotypes also reflect the underpinning convergence of deficits in multiple transmitter systems and pathways, including the cholinergic, noradrenergic, and serotonergic systems that occurs in PD.<sup>5, 6</sup>

In NMS dominant phenotypes, unlike typical PD, specific NMS such as cognitive impairment, depression, anxiety or dysautonomia dominate with variable overall NMS burden and motor symptoms. These NMS dominated subtypes described in Table 1 broadly conform to the emerging evidence of differential pathways of neuronal degeneration and Lewy body pathology in the central nervous system as proposed by several authors.( Figure 2) and spread of pathology as proposed by Beach et al (2009) and Braak et al (2003).<sup>2, 3, 14, 15</sup> NMS subtype patterns reflect phenotypes driven largely by dominant limbic, brainstem or cognitive involvement even at a very early motor stage of PD . In some PD phenotypes such as those with dominant dysautonomia or depression, there is evidence of specific biochemical disturbances (e.g adrenergic).<sup>16</sup>( Fig 2)

It is however important to note that PD is neither solely motor or non-motor, however, and naturally attempts to describe subtypes incorporating both aspects have been undertaken. Data-driven cluster analyses have led the way considering both motor and non-motor features for PD subtypes. Numerous cluster analyses have been published considering a wide variety of symptoms and signs. The results are heterogeneous, related to differences in variables entered into these analyses and the number of clusters sought, but data-driven

analyses have described subtypes that separate from each other most commonly on age at onset, or rate of progression, less commonly 'tremor dominance,' psychopathology, cognitive impairment or the presence or absence of motor complications.<sup>17-25</sup> When akinetic-rigid features and tremor are included in cluster analyses the emerging clusters have confirmed these aspects as defining features.<sup>23</sup> The relationship between non-motor symptoms and the empirical motor subtypes has also been explored by many different groups. We will summarize the current state of knowledge regarding non-motor symptoms in both empirical motor subtypes and data-driven classifications. First, we will consider the spectrum of non-motor features and why they may be particularly important in the evolution of PD.

#### The spectrum and relevance of non-motor features in PD

NMS are now recognised to be integral to the concept of Parkinson's disease (PD) and define the pre-motor stage while being variably present from onset of motor disease through to the end of the disease.<sup>26</sup>

Clinically, NMS comprise a range of clinical signs and symptoms resulting from multiple neurotransmitter deficiencies and differential rates of neurodegeneration within the central and the peripheral nervous system as well as the gut.<sup>27-29</sup> The range and nature of NMS of PD are wide and vary from cognitive and neuropsychiatric to sleep problems and dysautonomia either occurring in isolation as the dominant feature or in combination.<sup>27</sup> Motor aspects of PD such as falls may also be intricately linked to specific NMS of PD such as cognition.<sup>30</sup> Furthermore, some genetic variants of PD are thought to express specific NMS



while the clinical picture can be complicated by medication induced NMS such as impulse control disorders or dopamine agonist withdrawal syndromes.<sup>31</sup>

While a single dominant NMS such as apathy, pain or depression can have a major detrimental effect on patient and carer health related quality of life (HrQoL), recent studies indicate that in others the overall burden of a range of NMS that occur in PD could also be a key determinant of HrQoL.<sup>32,33</sup> The grading of the burden of NMS is now possible using validated MDS endorsed tools such as the NMS scale or questionnaire combining assessment with motor scores.<sup>34</sup> Thus, modern management of PD needs to take into account the heterogeneity and the burden of NMS in relation to outcome measures.

#### Non-motor features in empirical motor subtypes

Previous studies have examined both the overall number of non-motor symptoms and signs and the nature of non-motor symptoms and signs in tremor dominant compared with non-tremor dominant subtypes. At least three studies have explored this issue in newly diagnosed patients. Khoo et al.<sup>35</sup> found a greater number of non-motor symptoms associated with the PIGD phenotype among 159 newly diagnosed non-demented PD patients. When individual non-motor symptoms were examined, however, only sialorrhea was significantly more common in the PIGD subtype after Bonferroni correction.

Constipation, autonomic and sensory symptoms were found to be more common in the non-tremor dominant subtype by Müller et al.<sup>36</sup> In contrast, Pont-Sunyer et al. did not find a higher overall burden of non-motor symptoms in the akinetic-rigid phenotype (compared

with tremor-dominant individuals) within an incident PD cohort.<sup>37</sup> After adjustment for age and gender only constipation was significantly more common in the akinetic-rigid phenotype.

Using a putatively more sensitive approach, Herman et al. examined non-motor features distinguishing tremor dominant and PIGD subtypes.<sup>38</sup> They eliminated from their comparison individuals who had tremor/pigd ratios that fell close to the indeterminate range – thus they contrasted extreme cases. Using this approach they found that the PIGD group reported a larger number of non-motor symptoms on the Non-Motor Symptoms Questionnaire (NMS-Quest) and higher scores on the Scales for Outcomes in Parkinson's Autonomic (SCOPA-AUT) scale. They did not find differences in their cognitive performance, depression scores, olfactory identification or sleep quality. Taken together, autonomic features seem to be a common feature preferentially affecting individuals with non-tremor dominant PD-subtype, early in the disease.

Later in the disease, a different picture emerges, dominated by differences in the risk of cognitive impairment. Rajput et al. classified 166 individuals from a pathologically confirmed cohort as tremor dominant, mixed or akinetic-rigid subtype according to the predominant subtype over the entire course of the disease.<sup>39</sup> They found a higher cumulative incidence of dementia in the akinetic-rigid subtype of PD than either intermediate or tremor-dominant subtypes. Although there was no difference in survival, progression to Hoehn and Yahr stage 4 was faster in the akinetic-rigid subtype. A higher risk of cognitive dysfunction in the akinetic-rigid subtype has also been found by others.<sup>23,</sup>

<sup>40</sup> In cross sectional cohorts of variable disease duration affective symptoms<sup>23</sup> and olfactory dysfunction have also been shown to be more common in non-tremor dominant patients.<sup>41</sup>

Interpretation of studies is more straightforward when cohorts are studied at a uniform disease duration or longitudinally from the time of diagnosis. Many studies, however, have considered individuals at various durations of disease, or even incorporated measurements taken from individuals at various time points throughout their disease. In general differences have been found with all approaches.(Table 2)

Whether early or late in the disease non-tremor dominant subtypes have consistently been shown to have a broader array of non-motor symptoms. Early, autonomic features may predominate and later cognitive impairment is the most common non-motor issue.

#### Biomarkers distinguishing empirical motor subtypes: pathological, imaging and biochemical evidence

Clues to the biological basis of the clinical differences discussed above come from a number of biomarker and neuroimaging studies. Together, this literature provides substantial evidence for fundamental biological differences between tremor dominant and PIGD/akinetic-rigid subtypes.

For example, a small pathological study of brains of individuals with PD showed the lowest pallidal dopamine levels in individuals classified as having the akinetic-rigid subtype and they identified a distinct pattern of pallidal dopamine loss between the subtypes.<sup>42</sup> Disease duration varied widely across the individuals studied however, and was not reported by subtype so it is difficult to know whether or not the dopaminergic loss was related to the subtype *per se* or the more advanced disease process in these individuals. Patients who have minimal manifestations of PD other than tremor for prolonged periods (benign tremulous PD) have been shown to have less nigral cell loss than other forms of PD matched for age and disease duration at death.<sup>43</sup> Functional neuroimaging studies also suggest lower striatal dopaminergic and glucose metabolism in akinetic-rigid patients.<sup>44</sup> During a grip task, functional MRI also revealed reduced activation of the prefrontal cortex and globus pallidus of patients with nontremor-dominant PD compared with both patients with tremor-dominant PD and healthy controls.<sup>45</sup> In addition, a tremor-specific metabolic network has been identified by FDG PET scanning, indicating that parkinsonian tremor is mediated at least in part by a distinct metabolic network involving primarily cerebello-thalamo-cortical pathways.<sup>46</sup> The origin of this network abnormality is not well understood however; there is evidence that basal ganglia dopamine depletion drives the cerebello-thalamo-cortical abnormality.<sup>47</sup> This would seem at odds with the view that akinetic-rigid subtype has more severe pallidal dopamine depletion, suggesting a complex relationship between the cardinal manifestations of PD and basal ganglia dopamine depletion. Basal ganglia iron load as measured by magnetic resonance imaging has also been investigated as a potential distinguishing feature of the motor subtypes with conflicting results.<sup>48, 49</sup>

PIGD symptoms respond poorly to dopaminergic therapy and are thought to be mediated by non-dopaminergic mechanisms. It follows to wonder if other non-dopaminergic and non-motor features are more common in this subtype. Biomarker evidence for non-dopaminergic/non-motor differences between tremor dominant and PIGD/akinetic-rigid phenotypes includes that from CSF studies and cardiac  $^{123}\text{I}$ -metaiodobenzylguanidine (MIBG) scanning.

Schiess et al. examined cerebrospinal fluid neurotransmitter levels in tremor dominant, akinetic-rigid and mixed groups. They found that 5-hydroxyindolacetic acid and 5-hydroxytryptophan levels were lowest in the akinetic-rigid group while glutamate levels were highest. The authors propose that the low levels of 5-HIAA were consistent with higher rates of depression and cognitive dysfunction in the akinetic-rigid subtype<sup>9</sup> and overall indicating a more diffuse neurodegeneration encompassing non-dopaminergic systems.

On the basis of several lines of evidence linking PIGD phenotype to cognitive impairment and linking cognitive impairment in PD to altered CSF amyloid<sup>50</sup> or amyloid deposition,<sup>15, 51</sup> Alves et al. investigated CSF amyloid in PD motor phenotypes.<sup>52</sup> PD patients with the PIGD phenotype had significant alterations in several Abeta species, including those representing amyloid aggregation and deposition (Abeta42) and metabolism (Abeta38 and Abeta40), raising the possibility that amyloid pathology may underlie PIGD symptoms and that this may be mediated by alterations in amyloid beta metabolism. CSF Abeta markers correlated with PIGD scores independent of age, MRI white matter hyperintensities and cognition.

Several studies have examined the relationship between motor phenotype and cardiac  $^{123}\text{I}$ -MIBG uptake, in order to assess the integrity of the noradrenergic cardiac presynaptic sympathetic system, known to degenerate in PD. When groups have been comparable with respect to disease duration,  $^{123}\text{I}$ -MIBG uptake has been found to be lower in the akinetic-rigid or postural instability gait disorder subgroups, indicative of greater cardiac sympathetic denervation.<sup>53, 54</sup>

Taken together, biomarker studies of tremor dominant vs non-tremor dominant PD point towards non-tremor dominant PD as representing a more advanced and diffuse neurodegeneration than tremor dominant PD, encompassing dopaminergic and non-dopaminergic as well as synuclein and non-synuclein (A $\beta$ ) pathologies. This aligns with clinical studies that find a higher burden of non-motor symptoms in non-tremor dominant PD. The interpretation of this is not straightforward, however, in part because it is unclear whether or not tremor dominant or non-tremor dominance is a trait marking a fundamental distinction that endures throughout the course of PD or, alternatively, if it marks a state that may change. The latter is supported by the observation that many patients who begin with tremor dominant PD switch over time to PIGD or akinetic-rigid PD.<sup>55</sup>

### Non-motor features in data-driven classifications

Associations between non-motor features and the TD/PIGD phenotypes support the relevance of the motor subtypes in characterizing PD. On the other hand, if non-motor features do not associate with the motor phenotype then it argues that by basing our

classifications of PD patients solely on the motor phenotype we may be missing important heterogeneity. Liu et al examined the relationship between cluster assignments based on a data-driven approach incorporating motor and non-motor features (including mood, cognition, sleep quality, constipation and fatigue) in 138 patients with relatively early PD.<sup>21</sup> They found that the clusters emerging from their analysis did not bear a strong relationship to the empirical motor subtype of the patients. This suggests that the addition of non-motor features in defining subtypes may be important. Indeed, previous data-driven analyses have largely found that both motor and non-motor features constitute defining characteristics of the subtypes that emerge.<sup>19-24, 56, 57</sup>

With the improvement in our knowledge of the spectrum of non-motor features of PD, recent data-driven cluster analyses have investigated an expanded array of non-motor features and their contribution to PD subtypes. The use of comprehensive instruments to elicit non-motor features such as the NMSQuest<sup>58</sup> have facilitated this process. Importantly, recent studies have suggested that specific non-motor and non-dopaminergic symptoms may be particularly informative from a prognostic perspective. Erro et al. investigated the clustering of motor and non-motor features in a cohort of early, untreated PD patients.<sup>59</sup> They identified four clusters which they described as benign motor, benign mixed motor non-motor, non-motor dominant and motor dominant. In both of the clusters involving prominent non-motor features they identified a non-motor domain that was particularly affected. In the benign motor/non-motor group this was sexual symptoms and in the non-motor dominant group this was urinary symptoms. A longitudinal study assessing non-motor predictors of time to levodopa requirement found urinary symptoms

to have the greatest predictive power of a short time to levodopa.<sup>60</sup> Urinary symptoms were also associated with a greater burden of motor and non-motor symptoms both at baseline and follow-up. Thus both studies suggest that among early non-motor symptoms urinary dysfunction may suggest a more malignant course.

REM sleep behavior disorder (RBD) is another non-motor feature that has been suggested to have prognostic value. In cross-sectional analyses, RBD in PD has been associated with older age, male gender, orthostatic drop in blood pressure and orthostatic symptoms, non-tremor dominant motor phenotype, falls and depression.<sup>61</sup> Others have found that patients with RBD have lower cardiac <sup>123</sup>I MIBG uptake (presumably on the basis of premotor PD or diffuse Lewy body disease) even than individuals with early PD, indicative of early and more severe cardiac sympathetic dysfunction in those with RBD.<sup>62</sup> Further, RBD has also been defined as a cardinal feature of PD subtypes. Fereshtehnejad et al measured a comprehensive array of motor and non-motor features in PD patients including motor severity, motor complications, motor subtypes, quantitative motor tests, autonomic and psychiatric manifestations, olfaction, color vision, sleep parameters, and cognition.<sup>63</sup> The most discriminating baseline features between the three emerging clusters were mild cognitive impairment, orthostatic hypotension, and RBD. Upon follow-up, this cluster had more rapid progression of cognitive, motor and other non-motor domains. With respect to the prognostic value of RBD and the aforementioned urinary dysfunction it is notable that both are features of multiple system atrophy, a synucleinopathy known to be more quickly progressive and often misdiagnosed as PD early in its course. Whether or not these prognostic associations are related



to such misdiagnosis can only be revealed by longitudinal follow-up and/or pathological examination.

De Lau and colleagues assessed the relationship between subtypes and survival in a longitudinal study of over 400 PD patients and found the shortest survival in patients that had previously been classified into clusters characterized by the most non-motor and non-dopaminergic features (namely postural instability/gait disturbance, cognitive impairment, autonomic dysfunction, depression, and psychosis).<sup>56</sup> These studies identify non-motor symptoms as important markers of prognosis and important defining features of PD subtypes.

### Conclusions and Next Steps

To date, motor subtyping has dominated the landscape of biomarker research, possibly because its unidimensional nature and easily measured components make it more easily applied. Undeniably, the evidence suggests that there are important biological differences between the tremor-dominant and PIGD subtypes. However the mounting evidence for the relevance of non-motor features in PD subtypes behooves us to begin to investigate the biological underpinnings of subtypes defined by both motor and non-motor features. The current descriptions of specific NMS dominant phenotypes in untreated cohorts of PD and neuropathological heterogeneity of the disease process in PD further support the idea of non motor subtyping. This may be challenging, as PD subtypes are unlikely to be distinct, non-overlapping entities but are more likely to represent typical phenotypes within a

multidimensional spectrum resulting from variable contributions of a number of simultaneous pathological processes.

## **References**

Legend to Figure 1: Approaches to clinical subtyping in Parkinson's disease. Subtyping approaches can be divided into those that are empirically derived, from clinical observation, and data-driven based on co-occurrence of clinical features with no a priori hypothesis as to the way clinical features will cluster together.

Legend to Figure 2: Possible routes of spread of pathology in PD as described from pathophysiological studies and consequent phenotypic expression and non motor subtypes. RBD = rapid eye movement behaviour disorder, EDS = excessive daytime sleepiness, MCI = mild cognitive impairment. In some subtypes specific neurochemical deficits such as adrenergic, serotonergic, opioidergic and cholinergic pathways are preferentially involved sometimes greater than dopaminergic involvement.



= overlap between the phenotypes are possible.

Blue areas in cognitive phenotype diagram indicate frontal and parietal involvement with underpinning cholinergic dysfunction.

Fig adapted from Sauerbier et al.<sup>6</sup>.

Table 1 Clinical description of NMS dominant phenotypic variants in well characterized cohorts of PD (untreated and treated) as described in literature

(Adapted from Sauerbier et al. 2015)

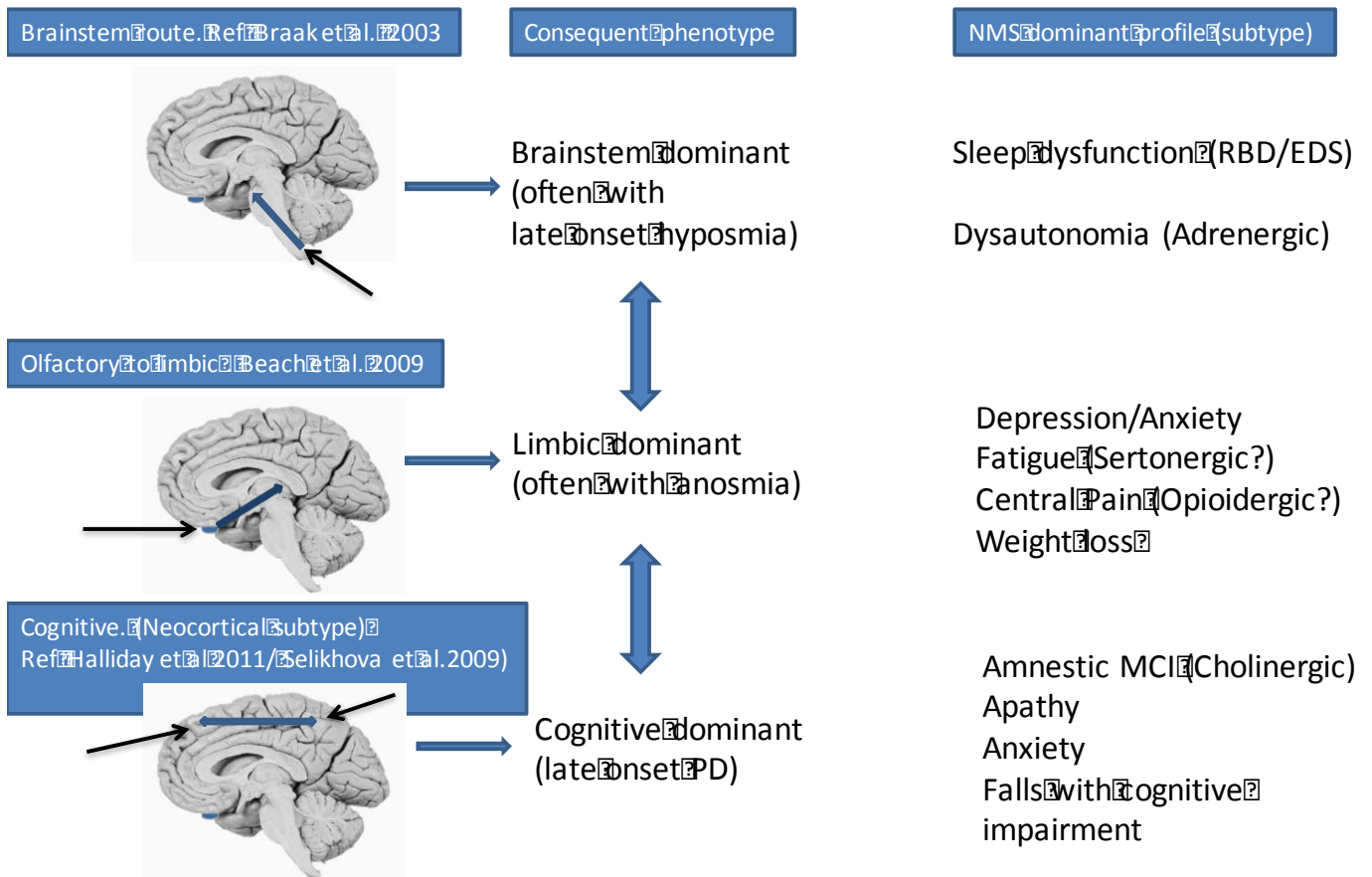
Non-motor domain	Defining features of subtype	Ancillary features
Cognitive <sup>30, 64, 65</sup>	Early and dominant cognitive dysfunction	<ul style="list-style-type: none"> <li>-Older age (<math>\geq 72</math> years)</li> <li>-Non-tremor dominant motor phenotype associated with falls</li> <li>-Poor semantic fluency score (<math>&lt;20</math>)</li> <li>-Lower pentagon copying score (<math>0 &lt; 1 &lt; 2</math>)</li> <li>-Microtubule-associated protein tau (MAPT) H1/H1 genotype possibly a biomarker</li> </ul>
Neuropsychiatric	Anxiety/depression. <sup>66, 67</sup>	
	A. Anxious-depressed	
	B. Depressed	-Postural instability gait disturbance
	C. Anxious	-Younger age Marked motor fluctuations
	Apathetic <sup>68</sup>	<ul style="list-style-type: none"> <li>-Relatively severe motor symptoms (out of proportion to disease duration)</li> <li>-Concomitant depression</li> <li>-Lower cognitive status</li> <li>-Fatigue</li> </ul>

		-Good response to dopaminergic drugs
Sleep	REM sleep behavior disorder <sup>61</sup>	<ul style="list-style-type: none"> <li>-Symmetric disease onset</li> <li>-Increased periods of freezing</li> <li>-Autonomic dysfunction</li> <li>-Prone to higher prevalence and severity of orthostatic symptoms</li> <li>-Higher rate of depression</li> <li>-Visual hallucinations</li> <li>-Increased frequency of falls</li> <li>-Impairment of colour vision</li> </ul>
Olfactory <sup>69</sup>	A. Severe loss of olfaction (anosmia)	<ul style="list-style-type: none"> <li>-dyskinesias</li> <li>-progressive weight loss</li> </ul>
	B. Moderate loss of olfaction	-no further weight loss with disease progression
Autonomic	Urinary dysfunction <sup>16</sup>	<ul style="list-style-type: none"> <li>-early noradrenergic deficit</li> <li>-postural hypotension</li> </ul>

Table 2: Studies examining non-motor symptoms in motor subtypes and their timing of defining motor subtype.

<b>Author, year</b>	<b>Mean Disease duration (SD) when motor subtype defined</b>	<b>NMS associated with PIGD or AR motor subtype</b>
Rajput 2009 <sup>39</sup>	Multiple observations throughout course	Cognitive dysfunction
Aarsland 2003 <sup>40</sup>	9.2 (5.9) years	Dementia (after prospective follow-up)
Muller 2011 <sup>36</sup>	2.3 (1.8) years Newly diagnosed, untreated	Autonomic and sensory symptoms
Reijnders 2009 <sup>23</sup>	Stavanger 9.0 (5.7) years Maastricht: 6.7 (5.0) years Single evaluation, variable disease duration	Cognitive dysfunction, depression, apathy
Stern 1994 <sup>41</sup>	Not reported. Single evaluation	Olfactory disturbance
Romenets 2012 <sup>61</sup>	Single evaluation variable disease duration With RBD 5.3 (3.9) Without RBD 6.3 (4.7)	RBD
Pont-Sunyer 2015 <sup>37</sup>	Median 11 months from motor symptom onset, 1 month from	Constipation

	diagnosis Single evaluation newly diagnosed untreated	
Khoo 2013 <sup>70</sup>	Median 4.4 months Single evaluation newly diagnosed untreated.	Greater number of NMS, sialorrhea
Herman 2014 <sup>38</sup>	PIGD: $5.7 \pm 3.7$ Tremor dominant: $5.4 \pm 3.2$ Single evaluation	Autonomic symptoms (SCOPA-AUT)





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